

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

APPLICANTS : M. Pamela GRIFFIN et al.  
SERIAL NO. : (Continuation of 09/271,279)  
FILED : Herewith  
FOR : METHOD AND APPARATUS FOR THE EARLY  
DIAGNOSIS OF SUBACUTE, POTENTIALLY  
CATASTROPHIC ILLNESS  
GROUP ART UNIT : 3762 (Anticipated)  
EXAMINER : K. Kamm (Anticipated)  
ASSISTANT COMMISSIONER  
FOR PATENTS  
Washington, D.C. 20231

**PRELIMINARY AMENDMENT**

SIR:

Prior to examination of the above-identified application, please make the amendments noted below.

**IN THE TITLE**

Change the title to read: --METHOD FOR THE EARLY DIAGNOSIS OF SUBACUTE, POTENTIALLY CATASTROPHIC ILLNESS --

**IN THE ABSTRACT OF THE INVENTION**

Please substitute the Abstract of the Invention enclosed on separate page for the present Abstract.

**IN THE SPECIFICATION**

After "TITLE OF THE INVENTION", insert the following paragraph:

--This application is a continuation of application Serial No. 09/271,279, filed March 17, 1999, the entire disclosure of which is incorporated by reference.--

Please substitute Figures 1-5 with attached corrected Figures 1-5 and amend the specification as follows:

Page 6, line 11: After "series" insert "--,--"; delete "and their frequency".

Page 6, line 12: Delete "histograms"; change "Figures 1E-IH" to "--Figures 1E--".

### **IN THE CLAIMS**

Please cancel Claims 1-38 and replace with new Claims 1-29.

Claim 1. A method for early detection of subacute, potentially catastrophic illness in an infant comprising:

- (a) monitoring heart rate variability in the infant;
- (b) identifying at least one characteristic abnormality in the heart rate variability; and
- (c) correlating the at least one abnormality with said illness.

Claim 2. The method of claim 1, wherein the illness is infectious.

Claim 3. The method of claim 2, wherein antibiotic therapy is initiated and a diagnostic work-up for the illness, comprising obtaining a blood culture from the infant, is provided when the at least one characteristic abnormality is identified.

Claim 4. The method of claim 2, wherein the illness is necrotizing enterocolitis.

Claim 5. The method of claim 4, wherein a diagnostic work-up for the illness, comprising an X-ray of the infant or a pathological specimen from the infant, is provided when the at least one characteristic abnormality is identified.

Claim 6. The method of claim 2 wherein the illness is selected from the group consisting of pneumonia, sepsis and meningitis.

Claim 7. The method of claim 1, wherein the at least one characteristic abnormality is identified from a normalized data set of RR intervals.

Claim 8. The method of claim 7, wherein the data set contains on the order of about  $10^3$  to  $10^4$  sequential RR intervals.

Claim 9. The method of claim 7, wherein the at least one characteristic abnormality is identified based on at least one of the third and higher moments of the data set.

Claim 10. The method of claim 9, wherein the at least one moment of the data set includes the skewness of the data set.

Claim 11. The method of claim 10, wherein the illness is sepsis or necrotizing enterocolitis.

Claim 12. The method of claim 9, wherein the at least one moment of the data set includes the kurtosis of the data set.

Claim 13. The method of claim 12, wherein the illness is sepsis or necrotizing enterocolitis.

Claim 14. The method of claim 7, wherein the at least one characteristic abnormality is identified based on at least one percentile value of the data set.

Claim 15. The method of claim 14, wherein the at least one percentile value is the 10th percentile value.

Claim 16. The method of claim 15, wherein the illness is sepsis or necrotizing enterocolitis.

Claim 17. The method of claim 7, wherein the at least one characteristic abnormality is identified based on the variance, standard deviation or coefficient of variation of the data set.

Claim 18. The method of claim 17, wherein the illness is sepsis or necrotizing enterocolitis.

Claim 19. The method of claim 10, further comprising a diagnostic work-up.

Claim 20. The method of claim 12, further comprising a diagnostic work-up.

Claim 21. The method of claim 15, further comprising a diagnostic work-up.

Claim 22. The method of claim 17, further comprising a diagnostic work-up.

Claim 23. The method of claim 1, wherein a diagnostic work-up is provided when the at least one characteristic abnormality is identified.

Claim 24. The method of claim 1 wherein the infant is a neonate.

Claim 25. A method for early detection of subacute, potentially catastrophic illness in an infant comprising:

- (a) monitoring the infant's RR intervals;
- (b) generating a normalized data set of the RR intervals;
- (c) calculating one or more of (i) moments of the data set selected from the third and higher moments and (ii) percentile values of the data set; and
- (d) identifying an abnormal heart rate variability associated with the illness based on one or more of the moments and the percentile values.

Claim 26. The method of claim 25, wherein the moments include the third moment of the data set.

Claim 27. The method of claim 25, wherein the moments include the fourth moment of the data set.

Claim 28. The method of claim 25, wherein the percentile values include the 10th percentile value.

Claim 29. The method of claim 25 wherein the infant is a neonate.

**REMARKS**

Claims 1-38 have been canceled and were replaced with new Claims 1-29. New Claims 1-29 are pending and being examined in this application.

Support for the new claims is found throughout the specification. In particular, the specification discloses that the claimed method can be used to predict the probability of an impending catastrophic clinical effect and can be applied in patient populations that are high at risk of such events. [Specification, p. 8, lines 23-27]

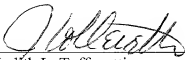
The Examiner is invited to contact the undersigned to discuss any matter concerning this application.

The Office is authorized to charge any fees or credit any overpayment under 37 C.F.R. § 1.16 or 1.17 to Deposit Account No. 11-0600.

Respectfully submitted,

KENYON & KENYON

Dated: Jan 29, 2001

  
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**ABSTRACT**

In one aspect of the invention, there is provided a method for early detection of subacute, potentially catastrophic illness in an infant. The method comprises: (a) monitoring heart rate variability in the infant; and (b) identifying at least one  
5 characteristic abnormality in the heart rate variability that is associated with the illness. This method can be used to diagnose illnesses such as, but not limited to, sepsis, necrotizing enterocolitis, pneumonia and meningitis. In another aspect of the present invention, there is provided a method for early detection of subacute, potentially catastrophic illness in an infant, which comprises: (a) monitoring the  
10 patient's RR intervals; (b) generating a normalized data set of the RR intervals; (c) calculating one or more of (i) moments of the data set selected from the third and higher moments and (ii) percentile values of the data set; and (d) identifying an abnormal heart rate variability associated with the illness based on one or more of the moments and the percentile values.

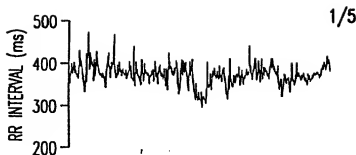


FIG.1A

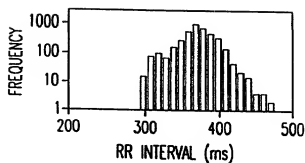


FIG.1E

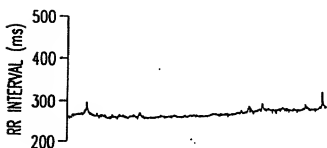


FIG.1B

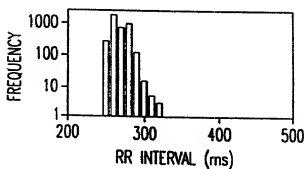


FIG.1E

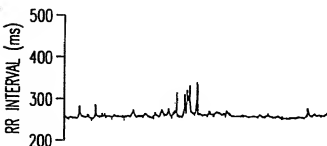


FIG.1C

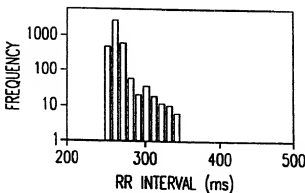


FIG.1E

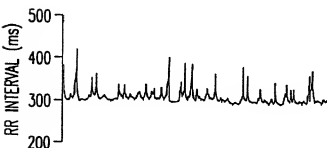


FIG.1D

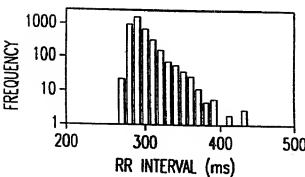


FIG.1E

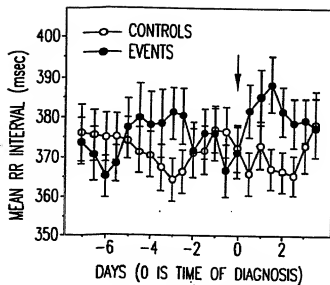


FIG.2A

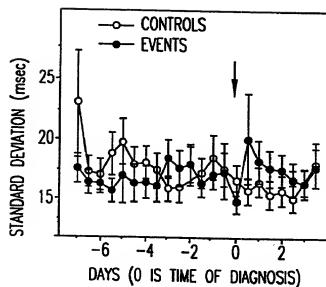


FIG.2B

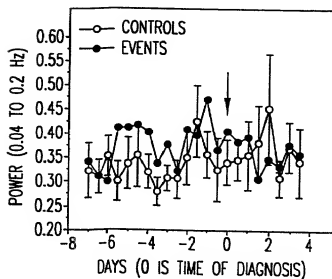


FIG.2C

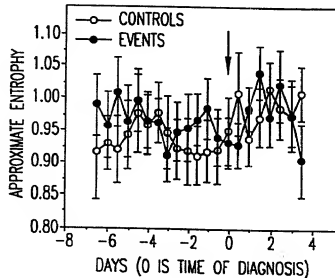


FIG.2D



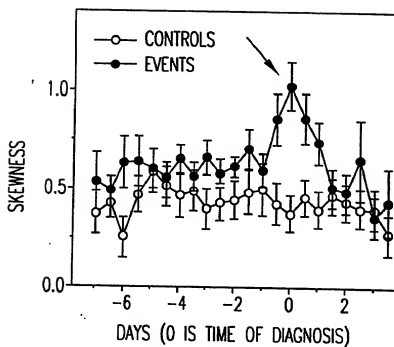


FIG.3A

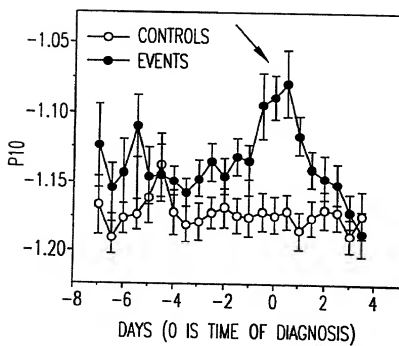


FIG.3B

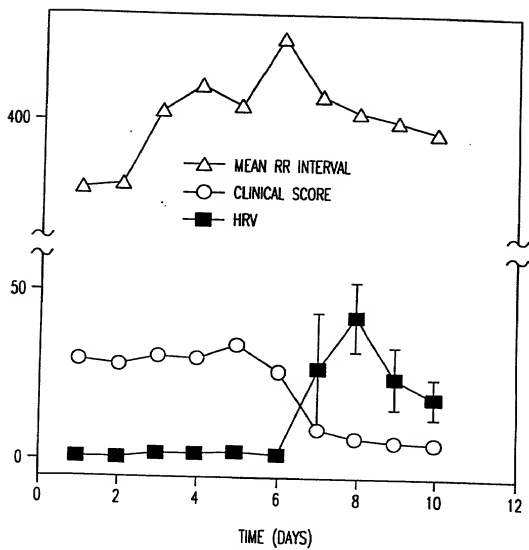


FIG.4

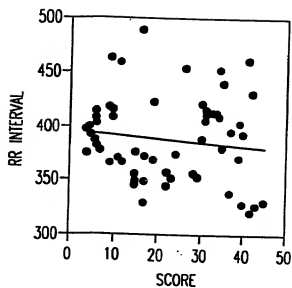


FIG.5A

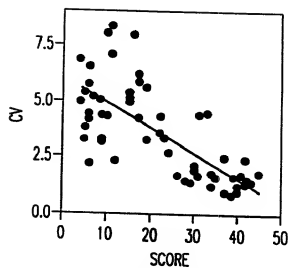


FIG.5B

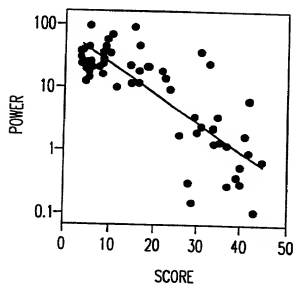


FIG.5C